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EXAMINER	
VENCI, DAVID J	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/621,958	LOCKE ET AL.	
	Examiner	Art Unit	
	David J. Venci	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *December 18, 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-14,17-23,33,34 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-14,17-23,33,34 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *December 18, 2007* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges Applicants' reply filed December 18, 2007. Claims 28, 32 and 35 are cancelled. Claims 4-14, 17-23, 33, 34 and 36 are pending and under examination in this application.

Specification

The disclosure is objected to because of the following informalities:

In paragraph [00126]:

In sentence 4, the commercial sources of the trademark "API III+" and the identity of the underlying equipment is vague. In addition, the identity of one or more objects referenced by the abbreviation "API" is not clear.

In paragraph [00127]: (*i.e.*, Table 2)

Table 2 fails to indicate whether Applicants used cyanoborohydride or cyanoborodeuteride, or how Applicants weighed the material in columns 3 and 4.

Appropriate correction is required.

Drawings

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

The drawings are objected to under 37 CFR 1.83(a). Specifically:

1. The lower panel of Fig. 8 fails to show "3-aminothiophenol labelled with CH_2O (m/z = 123.0) and CD_2O (m/z = 127.0) and $NaCNBH_3$" as described in the specification paragraph [00126], sentence 12 (need more mass). The identity of compounds detected in the lower panel of Fig. 8 is not clear because the expected mass for a methyl- or dimethyl- derivative of 3-aminothiophenol should be at least 139.193 and 153.193, respectively.

2. In Fig.10, the x-axis of the top spectrum does not appear to align with the x-axis of the bottom spectrum and/or one or more peak labels are "floating". For example, try to align the 1687.9 peak in both spectra.

3. In Fig.11, the x-axis of the top spectrum does not appear to align with the x-axis of the bottom spectrum and/or one or more peak labels are "floating". For example, the beginning of the top spectrum (*i.e.*, the smallest fragment farthest to the left) appears shifted 2-3 mass units to the right as compared to the beginning of the bottom spectrum.

Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-14, 17-23, 33, 34 and 36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.[1] The claims contain subject matter not described in the specification in a way to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Independent claims 33 and 36 are directed to "quantitative" methods requiring a ternary reaction comprising an amine-containing compound, an aldehyde and a reducing agent.

The specification provides minimal direction, or working examples, for enabling such "quantitative" methods.

Although Example 7 describes a labeling procedure involving a reducing agent[2] and an aldehyde, Example 7 does not describe the claimed ternary reaction because Example 7 appears to describe a different *two-step* labeling reaction requiring: (1) amino alkylation in an aldehyde, followed by (2) hydride reduction in acetonitrile and acetic acid. And although Example 7 labeled each amine compound at least two different ways (*i.e.*, CH_2O labeled, CD_2O labeled, *etc.*), the different amine compounds were analyzed

[1] According to the decision in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), the factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

separately and were not combined and analyzed together. Thus, Example 7 does not analyze a combined "3 to 8 samples" as claimed.

In addition, the data resulting from Example 7 suggests that the labeling procedure for some of the compounds may yield unpredictable results. Although Table 2 provides the number of milligrams of "compound" stuff introduced into Applicants' mass spectrometer, Table 2 does not disclose how each of the "compounds" were initially identified as CH_2O-labeled and CD_2O-labeled compounds, or how these CH_2O-labeled and CD_2O-labeled compounds were distinguished from other reactants and products present in each labeling reaction mixture. This uncertainty in measuring "compounds" may explain why the lower panel of Fig. 8 does not show "3-aminothiophenol labelled with CH_2O (m/z = 123.0) and CD_2O (m/z = 127.0) and $NaCNBH_3$", as described in Example 7.

Example 8 appears to describe the same *two-step* labeling procedure in Example 7. Similar to Example 7, Example 8 does not describe the claimed ternary reaction. And although Example 8 performed four different labeling steps, the four different labeling steps were performed on only one sample (*i.e.*, one "3-aminopyridine" sample). Thus, Example 8 does not analyze a combined "3 to 8 samples" as claimed.

Although Example 9 performed five different labeling steps, the five different labeling steps were performed on only one sample (*i.e.*, one "albumin" sample). And although the specification states the mass spectra resulting from Example 9 can be used for "identification" purposes, Example 9 does not appear to establish a general "identification" rule or procedure that is applicable to any "simultaneous quantitative analysis" beyond the analysis of one albumin sample of known concentration. Thus, Example 9 does not analyze a combined "3 to 8 samples" as claimed.

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[2] Examiner reiterates objection to Table 2 of Example 7 for not indicating whether Applicants used cyanoborohydride or

Finally, Examples 7-9 do not disclose reference standards and instrument-specific data treatment algorithms, both of which are necessary for skilled persons to meaningfully compare "quantitative" results. In addition, the commercial source and identity of the trademarked equipment "API III+" is vague.

In addition, the state of the prior art indicates a high level of unpredictability in "quantitative" mass spectrometry:

1. According to Carr & Annan, CURRENT PROTOCOLS IN PROTEIN SCIENCE, Unit 16.1, pp. 16.1.1-16.1.27, John Wiley & Sons, Inc. (1996), internal reference standards are required for "quantitative" mass spectrometry because data interpretation is affected by such factors as differing ionization efficiencies (see p. 16.1.15, right column, *Is MS data quantitative*), instrument-specific mass resolution (see paragraph bridging pp. 16.1.19 – 16.1.20), instrument-specific data treatment algorithms (see p. 16.1.21, paragraph bridging left and right columns) and adduct formation (see paragraph bridging pp. 16.1.21 – 16.1.22).

2. According to Robbins (US 5,939,229), mass spectrometer data interpretation is also affected by various isotope exchange reactions, thereby necessitating "predetermined"[3] reference standards (see Abstract).

3. Finally, Arend *et al.*, 37 ANGEW. CHEM. INT. ED. 1044 (1998), teach aldehyde-reductant labeling reagents might produce side-reactions with enol tautomers of carbonyl compounds (see Scheme 1) which might be present in complex analyte samples.

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cyanoborodeuteride, or how Applicants weighed the material in columns 3 and 4.

[3] See also, Croarkin & Tobias, NIST/SEMATECH e-Handbook of Statistical Methods, *available at* <http://www.itl.nist.gov/div898/handbook/>, (noting "[t]he most critical element of any measurement process is the relationship between a single measurement and the reference base for the unit of measurement").

Given the aforementioned deficiencies, Examiner posits that undue experimentation is required to remake and use Applicants' invention, as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 4-14, 17-23, 33, 34 and 36 are rejected under 35 U.S.C. 102(e) as being anticipated by Vandekerckhove & Gevaert (US 6,908,740). With respect to independent claim 36:

Vandekerckhove & Gevaert describe a method for analysis of up to 8 samples (see col. 21, line 60, "two or more samples") of cellular extracts (see col. 7, line 31, "prokaryotic or eukaryotic cell lysate"), wherein the molecules have an amine bearing an active hydrogen (see col. 24, line 37-62, "α—NH_2-group, or ε—NH_2 groups of lysines"), the method comprising:

(i)(ii) providing and adding amine-containing sample to acetaldehyde and reducing agent (see *e.g.*, col. 24, lines 37-62, "labeling procedures based on known chemical reactions", "Schiff's-base formation with deuterated acetaldehyde followed by reduction with normal or deuterated sodiumborohydride", "formaldehyde"), thereby producing an isotopically-labeled alkylamine derivative.

(iii) combining derivatives (see col. 22, line 4, "(c) combining");

(iv) separating derivatives into fractions (see col. 22, lines 6-7, "(d) separating the protein peptide mixture into fractions");

(v) enzymatically cleaving derivatives (see col. 22, lines 7-10, “(e) chemically, or enzymatically, or chemically and enzymatically altering at least one amino acid”; *see also*, col. 42, lines 52-53, “enzymatic cleavage”);

(vi) separating fragments (see col. 22, lines 10-11, “(f) isolating the flagged peptides”);

(vii) examining derivatives by mass spectrometry (see col. 22, lines 13-14, “(g) performing mass spectrometric analysis”); and

(viii) sequencing fragments (see col. 22, lines 17-18, “(i) determining the identity of the flagged peptide”).

Response to Arguments

Specification

In prior Office Action, paragraph [00126] was objected to because the commercial source of the trademark "API III+" and the identity of the underlying equipment is vague. In addition, the identity of one or more objects referenced by the abbreviation "API" is not clear.

In response, Applicants disclose that "API III+" is a product of MDS Analytical Technologies.

However, Examiner was unable to locate a "API III+" instrument on the website of MDS Analytical Technologies. The identity of the underlying equipment remains vague.

In prior Office Action, paragraph [00127] was objected to because Table 2 fails to indicate whether Applicants used cyanoborohydride or cyanoborodeuteride.

In response, Applicants argue that, according to the twelfth sentence of paragraph [00126], cyanoborohydride was used.

This argument is not persuasive because the twelfth sentence of paragraph [00126] appears to be describing Figure 8. In contrast, the first sentence of the paragraph [00126] describing the contents of Table 2 says "sodium cyanoborohydride or sodium cyanoborodeuteride" was used.

In prior Office Action, paragraph [00127] was objected to because Table 2 fails to indicate how Applicants weighed the material in columns 3 and 4.

In response, Applicants argue that the task of weighing samples is well within the skill of the art.

Although Examiner acknowledges that the task of weighing large items (*e.g.*, dried fruit) may be within the Art's skill set, nevertheless the task of weighing the compounds in Table 2 is complicated by the fact that each compound in Table 2 is the product of a unique derivatization reaction.

According to specification, paragraph [0071], first sentence, a co-requisite for "quantitative analysis" of labeled compounds, including those labeled compounds listed in Table 2, is a well-characterized and selective derivatization procedure. Although Table 2 provides the number of milligrams of "compound" stuff introduced into Applicants' mass spectrometer, Table 2 does not disclose how each of the "compounds" were initially identified as CH_2O-labeled and CD_2O-labeled compounds, or how these CH_2O-labeled and CD_2O-labeled compounds were distinguished from other reactants and products present in each labeling reaction mixture. Establishing procedures for initially identifying and distinguishing "compounds" in complex mixtures are some of the co-requisites for "quantitative analysis" of labeled compounds alluded to in paragraph [0071].

Claim Rejections - 35 USC § 112 – first paragraph

New Matter Rejection

In prior Office Action, claims 4-14, 17-23 and 32-36 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Specifically, Examiner was unable to locate support in Applicants' original specification for labeling reagents containing aldehyde AND reducing agent.

Applicants' direction in the specification is persuasive. Accordingly, this rejection is withdrawn.

Claim Rejections - 35 USC § 112 – first paragraph
Lack of Enablement

In prior Office Action, claims 4-14, 17-23, 33, 34 and 36 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

In response, Applicants appear to make the following arguments:

1. The specification paragraph [0081] describes how to use mass spectra to obtain quantitative results (see Applicants' reply, p. 14, second full paragraph).
    a. Applicants' method for "quantitative analysis" is predictable, in part because the specification paragraph [0080] describes how to use mass spectrometry with bovine serum albumin as a reference standard (see Applicants' reply, paragraph bridging pp. 1-15).
    b. Applicants' method for "quantitative analysis" is predictable, in part because Applicants' invention incorporates an internal reference standard (see Applicants' reply, p. 15, first full paragraph), as depicted in:
        i. Figure 10
        ii. Figure 13
2. Applicants' method for "quantitative analysis" is predictable, in part because the specification paragraph [0033] describes many different mass spectrometry methods (see Applicants' reply, p. 14, last full paragraph).
3. Applicants' method for "quantitative analysis" is predictable, in part because the same mass spectrometer ionizes peptides co-eluting from the same LC column with similar efficiency (see Applicants' reply, p. 15, second full paragraph).
4. The teachings of Robbins (US 5,939,229) concerning the confounding influence of isotope exchange reactions do not apply to the instant invention because isotope exchange reactions do

not occur with alkylamine derivatives of the present invention (see Applicants' reply, p. 15, penultimate paragraph).

5. The teachings of Arend *et al.*, 37 ANGEW. CHEM. INT. ED. 1044 (1998), concerning the confounding influence of side-labeling reactions with enol tautomers of carbonyl compounds do not apply to the instant invention because the instant invention does not involve a heating step and uses an amine to form a N-C bond (see Applicants' reply, p. 15, last paragraph).

Applicants' arguments have been carefully considered but are not persuasive.

With respect to argument 1), paragraph [0081] says mass spectra may be used to obtain "*relative* amounts" (emphasis added) between samples. Such comparison of "*relative* amounts" is not necessarily quantitative.

With respect to argument 1)(a), paragraph [0080] does not teach or suggest using bovine serum albumin as a reference standard. And, even assuming the specification disclosed a bovine serum albumin reference standard, the specification does not enable its use in the claimed invention.

With respect to argument 1)(b)(i), the scope of Applicants' argument does not appear commensurate to the scope of the claimed invention because Figure 10 and its accompanying text in the specification (see Example 9) do not analyze a combined "3 to 8 samples" as claimed. Rather, the information in Figure 10 was derived from a single "albumin" sample of known concentration. In addition, Examiner is unable to discern an "internal standard" in Figure 10 because all the albumin fragments came from albumin whose concentration was already known *a priori*.

With respect to argument 1)(b)(ii), the scope of Applicants' argument does not appear commensurate to the scope of the claimed invention because Figure 13 and its accompanying text in the specification (see Example 10) do not analyze a combined "3 to 8 samples" as claimed. Rather, the information in Figure 13 was derived from two samples of *C. Albicans*. And although Applicants could use Figure 13 to measure "*relative* amounts" of an enolase between the two samples, Figure 13 does not appear to establish a general "identification" rule or procedure that is applicable to any protein other than a *C. Albicans* enolase.

With respect to argument 2), paragraph [0033] mentions 7 different mass analyzers, each capable of coupling to one of 4 different ionization sources. However, it is not clear how this paragraph contributes to an enabling method on the one setup that Applicants actually used: an IonSpray triple-quadrupole setup. Further clarification is necessary.

With respect to argument 3), Carr & Annan probably were referring to *inter-instrument* variations in ionization efficiencies when describing the necessity of internal standards. However, Applicants' argument does not obviate the need for internal standards to control for *intra-assay* variations resulting from slight changes over time in analyte retention times.

With respect to argument 4), see specification paragraph [00113] which discloses the possibility of at least one isotope exchange reaction.

With respect to argument 5), Arend *et al.* describe a reaction that forms a N-C bond with an amine (see Scheme 1, top line, reaction step 2). Also similar to Arend *et al.*, the instant invention involves exothermic borohydride reductions which generate heat. Thus, the teachings of Arend *et al.* concerning the confounding influence of side-labeling reactions is relevant to the instant invention.

Claim Rejections - 35 USC § 102

In prior Office Action, claims 4-14, 17-23 and 32-36 were rejected under 35 U.S.C. 102(e) as being anticipated by Aebersold *et al*. (US 6,670,194).

In response, Applicants argue that the "B" in the "B-N(CD_3)[line break]CD_2CO— conjugate" recited at col. 25, lines 48-49 of Aebersold *et al*. (US 6,670,194) and cited in the prior Office Action refers to "Biotin" rather than Examiner's "Boron". Applicants' argument is persuasive. Accordingly, this rejection is withdrawn.

In prior Office Action, claims 4-14, 17-23, 33, 34 and 36 were rejected under 35 U.S.C. 102(e) as being anticipated by Vandekerckhove & Gevaert (US 6,908,740).

In response, Applicants argue that, although Vandekerckhove & Gevaert perform Applicants' labeling procedure with two samples, Vandekerckhove & Gevaert do not enable this procedure for simultaneously analyzing "3 to 8 samples" as claimed (see Applicants' reply, p. 18, heading "2. Vandekerckhove & Gevaert").

Applicants' argument is not persuasive because Vandekerckhove & Gevaert describe and enable methods for both: 1) performing Applicants' labeling chemistry; or 2) analyzing "3 to 8 samples". In column 24, lines 37-62, Vandekerckhove & Gevaert describe Applicants' labeling chemistry using acetaldehyde and sodiumborohydride reducing agent. Also, Vandekerckhove & Gevaert describe a procedure for analyzing "3 to 8 samples", wherein multiple peptide fractions are isolated from an HPLC column, and are then recombined with each other for subsequent separation, spectrometry, labeling,

recombination, etc. (see columns 64-67 and Tables IVA, IVB, IVC, V and VII). Thus, Vandekerckhove & Gevaert describe all the elements of Applicants' invention, as claimed.

Conclusion

No claims are allowable at this time.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Venci whose telephone number is (571)272-2879. The examiner can normally be reached on 08:00 - 16:30 (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

David J Venci
Assistant Examiner
Art Unit 1641

/Long V Le/
Supervisory Patent Examiner, Art Unit 1641